C3

PHASE 3 SUMMARY OF MRID 00094012:

6-MONTH TOXICITY STUDY IN DOGS

STUDY # 1628

FLUMETRALIN

GUIDELINE REFERENCE:

82-1(B) 90-DAY FEEDING - NONRODENT

SUMMARY PREPARED BY:

JACQUELINE GILLIS, Ph.D.

MERRILL TISDEL

5 OCTOBER 1990

ORIGINAL STUDY PREPARED BY:

ELARS BIORESEARCH LABORATORIES, INC.

FORT COLLINS, COLORADO

C3

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA §10(d)(1)(A), (B), or (C).

Company: CIBA-GEIGY Corporation (Typed Name)

Company Agent: Thomas Parshley (Typed Name)

Title: Senior Reg. Specialist

Signature: _____ Date: _____

These data are the property of the Agricultural Division of CIBA-GEIGY Corporation, and as such, are considered to be confidential for all purposes other than compliance with FIFRA §10. Submission of these data in compliance with FIFRA does not constitute a waiver of any right to confidentiality which may exist under any other statute or in any other country.

C3

GOOD LABORATORY PRACTICE STATEMENT

ELARS Research Laboratories is no longer in business. Therefore, a GLP statement cannot be obtained from a study director or laboratory management. The attached page from the report on this study indicates that the study was conducted under FDA Good Laboratory Practice Regulations (21 CFR 58).

GOOD LABORATORY PRACTICE STATEMENT

This study does not meet the requirements for 40 CFR Part 160 (see above).

Submitter/Sponsor of Study: Merrill Tisdel

Merrill Tisdel
Agricultural Division
CIBA-GEIGY Corporation
Greensboro, North Carolina

F403SW0913MT.1

June 29, 1981	Blood collection
July 7, 1981	Necropsy
July 9, 1981	Dosing Daily observations
July 13, 1981	Quality Assurance inspection report issued to management and the study director
August 14, 1981	Feed mixing
August 24, 1981	Weighing of dogs Feed consumption determinations Dosing Daily observations
August 26, 1981	Blood collection
August 31, 1981	Urinalysis determinations Necropsy
September 4, 1981	Cutting in tissues in pathology
September 14, 1981	Quality Assurance inspection report issued to management and the study director
November 24, 1981	The final report was reviewed and found to reflect accurately the raw data.

This study was conducted in compliance with the FDA Good Laboratory Practice Regulations (Federal Register, Vol. 43, December 22, 1978) and in accordance with the EPA "Proposed Guidelines For Registering Pesticides in the U.S., Hazard Evaluation: Human and Domestic Animals" (Federal Register, Vol. 43, August 22, 1978).

Dawn M. Needles 11/24/81
Dawn M. Needles
Quality Assurance

C3

Certification of Availability of Raw Data

I hereby certify that the submitter possesses or has access to the raw data used in or generated by the study summarized in this document.

Submitter's Representative:

Signature/Date: Merrill Tisdel 10.15.90

Typed Name: Merrill Tisdel

Title: Toxicologist

Certification of Accuracy of Summary and Adequacy of the Study

I certify, in compliance with FIFRA section 4(e)(1)(A), that this summary accurately represents the data presented in the report(s) of this study cited by MRID, and that this study fully satisfies all pertinent requirements of the OPP Guideline it addresses.

Submitter's Representative:

Signature/Date: Merrill Tisdel 10.15.90

Typed Name: Merrill Tisdel

Title: Toxicologist

R406MT0628MG

C3

82-1 Subchronic Feeding in the Rodent and Nonrodent

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1. Y Technical form of the active ingredient tested.
2. Y At least 10 rodents or 4 nonrodents/sex/group (3 test groups and control group).
3. Y/N Dosing duration daily for 90-days or 5 days/week for 13 weeks.
4. Y/N Doses tested include signs of toxicity at high dose but no lethality in nonrodents or a limit dose if nontoxic (1000 mg/kg).
5. Y Doses tested include a NOEL.
6. * Y Analysis for test material stability, homogeneity and concentration in dosing medium
7. Y Individual daily observations.
8. Y Individual body weights.
9. Y Individual or cage food consumption.
10. * Y Opthalmoscopic examination (at least pretest and at term) control and high dose.
11. Y Clinical pathology data of 12 & 13 at termination for rodents; for nonrodents at the beginning then either monthly or midway and at termination.
12. Y Hematology.
    - Y Erythrocyte count
    - Y Hemoglobin
    - Y Hematocrit
    - Y Leucocyte count
    - * Y Differential count
    - Y Platelet count (or clotting measure)
13. Y Clinical chemistry.
    - * Y Alkaline phosphatase
    - Y Aspartate aminotransferase
    - * N Creatinine kinase
    - Y Alanine aminotransferase
    - * Y Lactic dehydrogenase
    - Y Glucose
    - Y Bilirubin
    - * Y Cholesterol
    - * N Creatinine
    - Y Total Protein
    - N Albumin
    - Y Urea nitrogen
    - N Inorganic phosphate
    - Y Calcium
    - * Y Potassium
    - Y Sodium
    - * N Chloride
14. * Y Urinalysis, only when indicated by expected or observed activity. As scheduled in 11.
    - N Blood
    - Y Protein
    - Y Ketone bodies
    - N Appearance
    - Y Glucose
    - Y Total bilirubin
    - * Y Urobilirubin
    - Y Sediment
    - Y Specific gravity (osmolality)
    - * N Volume
15. Y Individual necropsy of all animals.

Criteria marked with a * are supplemental and may not be required for every study.

16. Y Histopathology of the following tissues performed on all nonrodents and rodents, all control and high dose animals, all animals that died or were killed on study, all gross lesions on all animals, target organs on all animals and lungs, liver and kidneys on all other animals.

Y aorta	Y jejunum	Y peripheral nerve
Y eyes	Y bone marrow	Y kidneys†
Y caecum	Y liver†	Y esophagus
Y colon	Y lung	Y ovaries
Y duodenum	Y lymph nodes	N oviduct
Y brain†	Y stomach	Y pancreas
Y skin	Y mammary gland	N rectum
Y heart	Y spleen	Y spinal cord (3x)
Y testes†	Y musculature	Y thyroid / parathyroids
Y pituitary	Y epididymis	Y salivary glands
Y ileum	Y adrenals	Y thymus
Y trachea	Y urinary bladder	
Y gall bladder	Y accessory sex organs; uterus	

† organs to be weighed

Criteria marked with a * are supplemental and may not be required for every study.

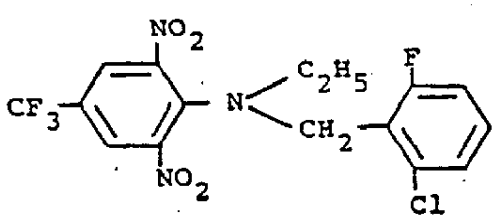
C3

IDENTIFICATION OF TEST MATERIAL

Chemical Name

CAS Name:	N-(2-Chloro-6-fluorobenzyl)-N-ethyl-α,α,α,-trifluoro-2,6-dinitro-p-toluidine or 2-Chloro-N-[2,6-dinitro-4-(trifluoromethyl)phenyl]-N-ethyl-6-fluorobenzenemethanamine
Common Name:	Flumetralin
Trade Name:	Prime +®
CIBA-GEIGY Code Number:	CGA-41065
CAS Registry Number:	62924-70-3
EPA Shaughnessy Number:	Unknown

Chemical Structure:



Percent Active Ingredient

92% minimum

PM3006899743

C3

Flumetralin: 82-1(B): Subchronic Feeding in the Nonrodent

1. The test article was Flumetralin (CGA-41065) Technical, a bright orange crystalline substance, FL-810009, purity 96.4%.

2. There were eight male and eight female purebred Beagle dogs in the control and high-dose groups. There were six males and six females in the low- and mid-dose groups.

3. Animals in the three test groups were administered the test article in feed daily for a total of six months. Animals in the control group were fed the basal diet mixed with the vehicle (acetone) for the same six months.

4. The doses tested were 0 (control), 30 ppm, 300 ppm, and 3000 ppm. Six animals died or were sacrificed moribund while on study, one in the low-dose group, one in the mid-dose group, and four in the high-dose group. It was concluded that the low-dose animal died from a very acute infectious process and that the other five dogs died from a similar but more chronic infectious process which was probably exacerbated by consumption of the test material. Body weights and body weight gains for the 3000 ppm animals were severely reduced when compared to the controls. Weight gains for the 300 ppm animals were within an anticipated normal range but were somewhat lower than the controls. Food consumption values were consistently lower for the 3000 ppm animals when compared to the controls. Clinical pathology parameters were affected in 3000 ppm animals: erythroid parameters were consistently decreased, and reticulocyte counts, platelet counts, and Heinz bodies were increased; WBC counts and methemoglobin were consistently higher in males; elevated clinical chemistry parameters included alkaline phosphatase, cholesterol, LDH, and potassium. Absolute and relative liver and spleen weights were increased in 3000 ppm animals. Abnormal necropsy findings in the liver and yellow discoloration and/or reduced body fat were noted in 3000 ppm animals. Histopathologic findings in the livers of 3000 ppm animals included bile duct proliferation, pericholangeal fibrosis, hemosiderosis, hepatocellular necrosis, and multifocal inflammation. Lymphoid depletion in the spleen of high-dose dogs was also considered treatment-related.

C3

5. The no-observable-effect level for all of the parameters assessed in the study was 30 ppm.

6. Test article concentration in the diets was assessed for 13 batches of diets prepared during the course of the study. Analytical concentrations were consistently within -10% to +15% of target concentrations for the three dietary doses. Homogeneity was assessed at the initiation of the study and the diets were found to be acceptably homogenous. Stability of the test article in 30 ppm and 3000 ppm diets was determined to be at least 46 days at room temperature (within 6% of target concentration).

7. All animals were observed daily for mortality and signs of pharmacological and/or toxicological effects. Six animals died or were sacrificed moribund while on study: one in the low-dose group (Week 4), one in the mid-dose group (Week 25), and four in the high-dose group (three during Week 6, one during Week 19). Except for the low-dose animal, these dogs had progressive weight loss, anorexia, pyrexia, dehydration, and depression. It was concluded that the low-dose animal died from an acute infectious process and that the other five dogs died from a more chronic infectious process which had been exacerbated by test material administration. No treatment-related changes were observed in dogs which survived the study period. Incidental observations which included emesis, soft stool, diarrhea, and lacrimation were observed with similar frequencies in all groups.

8. Individual body weights were recorded weekly. For high-dose males and females, mean body weights were consistently lower than any other group throughout the study, when either including or excluding animals which died or were sacrificed moribund. High-dose males had significantly lower weight gains than controls for Weeks 2-10, 17, 21-24, and 26. High-dose females had significantly lower weight gains than controls for Weeks 3, 4, 11, 13, 14, and 17-26. Mean body weights and weight gains tabled below do not include data from dogs which died or were sacrificed moribund. Weight gains for the 3000 ppm animals were severely reduced when compared to controls. Both males and females lost weight between 13 and 26 weeks, and females showed an overall weight loss from initiation. Animals in the 300 ppm group had more normal weights and weight gains, but cumulative weight gains at 13 and 26 weeks were consistently lower than controls by 17% or more.

C3

Dose Group	Body Weight (kg) Week 0	Week 13	Week 26	Weight Gain (% of Control) Week 13		Week 26	
Males							
Control	9.55	12.81	13.41	3.26		3.86	
30 ppm	9.48	12.42	12.33	2.94	(90)	2.85	(74)
300 ppm	9.76	12.06	12.32	2.30	(71)	2.56	(66)
3000 ppm	9.92	11.62	11.23	1.70	(52)	1.31	(34)
Females							
Control	7.86	9.75	9.92	1.89		2.06	
30 ppm	8.12	10.38	10.42	2.26	(120)	2.30	(112)
300 ppm	7.80	9.28	9.50	1.48	(78)	1.70	(83)
3000 ppm	8.55	8.93	8.37	0.38	(20)	-0.18	--

9. Food consumption data were recorded weekly. For high-dose males and females, food consumption was consistently lower than any other group throughout the study. These differences were statistically significant for males during 18 out of the 26 study weeks, but significant for females at Week 1 only.

10. Ophthalmoscopic examinations were performed prior to dosing and at approximately 180 days on study. The findings noted were sporadic and common in animals of this age. There were no treatment-related findings.

11. Hematology and clinical chemistry data were collected on all animals prior to the initiation of dosing and at 30-day intervals thereafter. Urinalysis data were collected on all animals prior to the initiation of dosing and at 60-day intervals thereafter. See Items 12, 13, and 14 for results.

12. Hematology measures were erythrocyte count, hematocrit, hemoglobin, platelet count, activated partial thromboplastin time, prothrombin time, total and differential leukocyte counts, methemoglobin, Heinz bodies, and, when evidence of anemia was observed, reticulocyte count. Differences in erythroid parameters between high-dose males and females and their respective controls included consistently decreased erythrocyte count, hematocrit, hemoglobin, and mean corpuscular hemoglobin volume, and increased platelets, reticulocyte count, and Heinz bodies. Also, leukocyte count and methemoglobin were consistently higher in high-dose males and females than their respective controls. These differences were found at all six assessment times and were often statistically significant. Intermediate-dose males had slightly but significantly lower erythrocyte counts and hemoglobin than controls at the Day 150 assessment.

C3

13. Clinical chemistry measures were total protein, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactic dehydrogenase, glucose, urea nitrogen, total bilirubin, total cholesterol, calcium, potassium, and sodium. Alkaline phosphatase levels in high-dose males and females were significantly and markedly higher than their respective controls from Day 60 through study termination. Levels of cholesterol in high-dose males and females were significantly higher than controls throughout the study. Cholesterol levels tended to be higher for the 300 ppm animals, but the differences were generally not statistically significant. High-dose males and females had consistently higher LDH levels than their controls; these differences were statistically significant at three of six time intervals for females. Also, levels of potassium were slightly elevated and statistically significant for half of the time intervals for high-dose males and females, but were within historical control ranges. Sporadic differences in calcium, sodium, alanine aminotransferase, and aspartate aminotransferase were not considered to be biologically significant.

14. Urinalysis measures were protein, glucose, specific gravity, pH, ketones, bilirubin, urobilinogen, and microscopic examination of formed elements. No differences were apparent between test groups and controls for any of the parameters at any time interval.

15. Animals which survived until study termination were sacrificed at the scheduled terminal sacrifice by exsanguination by cardiac puncture under sodium phenobarbital anesthesia. A gross necropsy examination was performed on sacrificed animals and the six animals which died or were sacrificed moribund during the course of the study. Weights were obtained for liver, kidneys, heart, brain, spleen, gonads, adrenal glands, thyroid glands (with parathyroids), and pituitary gland. Tissue portions of adrenal gland, aorta, bone marrow, brain (cerebrum, cerebellum, pons), cecum, colon, esophagus, eyes with optic nerve, gallbladder, heart, kidney, lung with mainstem bronchi, cervical and mesenteric lymph nodes, mammary gland, muscle, ovaries, pancreas, sciatic nerve, pituitary, prostate, submandibular salivary gland, skin, small intestine (duodenum, jejunum, ileum), spinal cord, spleen, stomach (cardia, fundus, pylorus), testes with epididymides, thymus, thyroid with parathyroid, trachea, urinary bladder, uterus (corpus and cervix), and any tissues with gross lesions were obtained from each animal. The tissues were fixed in 10% buffered formalin (eyes and testes in Bouin's solution), embedded in paraffin, sectioned at 4-5 µm, and stained with hematoxylin and eosin.

For high-dose males and females, absolute liver weight, liver/body weight ratio, and liver/brain weight ratio were significantly higher than controls. High-dose males and females also had higher absolute spleen weight, spleen/body weight ratio, and spleen/brain weight ratio. Several other organ/body weight ratios showed significant differences, but were not considered to be related to treatment.

Treatment-related gross necropsy findings in high-dose males and females were general atrophy of body fat, yellow discoloration of body fat, and roughened and/or mottled and/or firm liver. High-dose females also showed enlarged lymph node(s).

16. Histopathologic examinations were performed on all preserved tissues of all animals. In high-dose animals, treatment-related findings of bile duct proliferation, pericholangeal fibrosis, hemosiderosis, hepatocellular necrosis, and multifocal inflammation in the liver were found to correspond with the gross necropsy findings. Lymphoid depletion in the spleen was noted in most high-dose dogs and was considered treatment-related. Myeloid hyperplasia noted in some high-dose dogs was considered to be related to the borderline regenerative anemia in these dogs.

17. There were no significant changes from the Acceptance Criteria in this study. Five deviations from the Acceptance Criteria are noted. Under Item 3, the study was conducted for six months rather than for 90 days. This deviation is considered to be insignificant because the treatment duration exceeded the requirement. Under Item 4, although mortalities occurred, they were not considered directly related to treatment. The one mortality at the low dose was attributed to an acute infectious process and not related to treatment. The other mortalities may have been indirectly related to treatment, in that an existing infectious process was exacerbated. In addition, there were at least five dogs per sex in each group, which exceeded the requirement and was enough to evaluate toxicity. Under Item 13, five clinical chemistry parameters, creatinine kinase, creatinine, albumin, inorganic phosphate, and chloride, were not assessed. Under Item 14, blood, appearance, and volume of urine were not assessed. Under Item 16, oviduct and rectum were not examined histologically. These deviations are considered to be insignificant because none of the study data indicated that additional data from these parameters would have aided in identifying target organs or effect levels.